



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US93/04454 <b>(22) International Filing Date:</b> 12 May 1993 (12.05.93)  <b>(30) Priority data:</b> 07/882,223                      13 May 1992 (13.05.92)                      US  <b>(71) Applicant:</b> THE UNITED STATES OF AMERICA, as represented by THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Box OTT, Bethesda, MD 20892 (US).  <b>(72) Inventors:</b> MYERS, Charles ; 11111 Ralston Road, Rockville, MD 20852 (US). TREPEL, Jane ; 5121 Wissioming Road, Bethesda, MD 20816 (US). KANG, Won, Ki ; 243 Congressional Lane, Rockville, MD 20852 (US). WHITESELL, Luke ; 6006 Kingsford Road, Bethesda, MD 20817 (US). NECKERS, Len ; 5121 Wissioming Road, Bethesda, MD 20816 (US).		<b>(74) Agents:</b> WEBER, Kenneth, A. et al.; Townsend and Townsend Khourie and Crew, Steuart Street Tower, 20th Floor, One Market Plaza, San Francisco, CA 94105 (US).  <b>(81) Designated States:</b> AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> USE OF INHIBITORS OF 3-HYDROXY-3-METHYLGLUTARYL COENZYME A REDUCTASE AS A MODALITY IN CANCER THERAPY  <b>(57) Abstract</b>  Methods of treating various cancers, such as prostatic adenocarcinoma, with inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG Co-A), such as lovastatin, are provided. Dosing ranges, schedules and toxicities are included.		

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5        USE OF INHIBITORS OF 3-HYDROXY-3-METHYLGLUTARYL COENZYME A  
         REDUCTASE AS A MODALITY IN CANCER THERAPY

                    BACKGROUND OF THE INVENTION

10        The invention relates generally to use of inhibitors  
         of 3-hydroxy-3-methylglutaryl coenzyme A reductase in treating  
         cancer. More specifically the invention relates to use of  
         lovastatin and its homologues or analogues to treat human  
         adenocarcinoma and selected sarcomas.

15        Metastatic prostate cancer and stomach cancer are  
         refractory to all available cytotoxic agents. There is no  
         curative medical therapy for these common adult carcinomas.  
         Lovastatin, widely used for treatment of hypercholesterolemia,  
         is generally believed to be useful for synchronizing tumor  
20        cell growth in one cell cycle phase. Although there exist  
         scattered reports of the cytotoxic activity of lovastatin, it  
         has not been pursued as an anticancer drug.

         Adenocarcinoma is a group in the histological  
         classification of cancer. For instance, 95% of prostate  
         carcinomas are adenocarcinomas. Cancers of the stomach,  
25        intestine and colon are almost always adenocarcinomas, as are  
         gall bladder cancers. Breast cancer is also an adenocarcinoma  
         in perhaps 90% of the cases. Cancer of the esophagus is  
         adenocarcinoma in about 10%-15% of cases and adenocarcinoma of  
         the lung represents about 30% of pulmonary cancers.

30        One of the challenges in treating cancer is the  
         ability to follow the course of the disease and the efficacy  
         of therapy with some objective marker. Ideally, the marker  
         would be obtainable by either noninvasive or minimally  
         invasive means such as a blood test. The marker may be useful  
35        in diagnosing a type of cancer as well as in evaluating the  
         prescribed therapy.

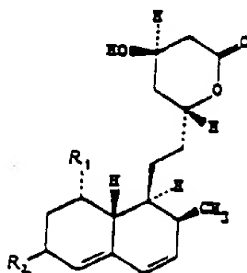
         An example of a tumor marker is prostate specific  
         antigen (PSA). Serum PSA is clinically useful to monitor the

therapeutic response of prostatic cancer patients. See Hudson et al., Clinical Use of Prostate Specific Antigen in Patients With Prostate Cancer, *Journal of Urology* 142:1011-1017 (October 1989).

5           Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG Co-A) are known. HMG Co-A catalyzes a crucial step in the biosynthesis of cholesterol. Inhibitors of this enzyme are well known as cholesterol lowering agents. See United States Patent 3,983,140 to Endo et al which is  
10           incorporated by reference herein. Examples of these inhibitors include the group of physiologic active substances ML-236. Compactin (ML-236B) is a member of this group, and it has been isolated from cultures of *Penicillium brevicompactum* and *Penicillium citrinum*. See '140 to Endo et al. See also  
15           Brown et al, Crystal and Molecular Structure of Compactin, a New Antifungal Metabolite From *Penicillium Brevicompactum*, *Journal Chemical Society Perkins Trans. I* 1165-1170 (1976).

          The structures of compactin and some of its homologues are well characterized, and their total synthesis  
20           has been achieved by a number of groups. See for example Grieco et al, Total Synthesis of the Hypocholesterolemic Agent Compactin, *Journal American Chemical Society* 105:1403-1404 (1983), Wang et al, Total Synthesis of Compactin (ML-236B), *Journal American Chemical Society* 103:6538-6539 (1981), and  
25           Hsu et al, Total Synthesis of the Hypocholesterolemic Agent Compactin, *Journal American Chemical Society* 105:593-601 (1983).

          The structural formula of some of the known inhibitors of HMG Co-A is represented by formula I



wherein R<sub>1</sub> is a hydrogen atom, a hydroxy group, a 2-methylbutyryloxy group (-OCOCH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>) or a 2,2-

dimethylbutyryloxy group ( $-\text{OCOC}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$ ) and  $\text{R}_2$  is a hydrogen atom or a methyl group. In lovastatin,  $\text{R}_1$  is a 2-methylbutyryloxy group and  $\text{R}_2$  is a methyl group. In the compound mevastatin,  $\text{R}_1$  is a methyl group and  $\text{R}_2$  is a hydrogen atom. Simvastatin has a 2,2-dimethylbutyryloxy group in the  $\text{R}_1$  position and a methyl group in the  $\text{R}_2$  position.

A number of therapeutic measures, such as surgical excision, chemotherapy and radiation, are available in cancer therapy. Frequently, a combination regimen using more than one of the above-mentioned modalities is employed. Additionally, an array of chemotherapeutic agents may be used in treating any one cancer patient. If a tumor marker is available, then knowledge of its abundance may help the clinician tailor the therapeutic regimen. For example, if a patient suffering from prostatic carcinoma receives a drug which lowers his PSA, then the clinician may conclude that the tumor is regressing. Thus, he will alter the patient's therapy accordingly.

#### SUMMARY OF THE INVENTION

The invention provides a method for treating mammalian adenocarcinomas and sarcomas comprising administration of an effective amount of an inhibitor of HMG Co-A or homologues of the inhibitor. Adenocarcinoma is known to afflict the prostate, stomach, lung, breasts and colon, as well as other sites. An example of a sarcoma within the meaning of the present invention is Ewing's sarcoma, which is a medullary bone tumor typically attacking the long bones.

"Homologue(s)" refers to compounds of similar chemical structure but which have different radicals or side groups substituted. The term is further meant to include analogues or compounds with similar electronic structures but different atoms; isolog is a synonym. When referring to treating a cancer, improved or decreased symptoms are included. That is, "treatment" is not limited to an objective regression of tumor size, but also includes the patient's report of his subjective status.

An effective amount of the compound is that amount which provides either subjective relief of symptoms or decrease in the tumor burden or decrease in an identifiable tumor marker. Administration of the compound is by any medically or pharmaceutically accepted route. Typically, the oral route is preferred. The dosing range is preferably from about 2.0 to about 52.0 mg/kg/day based on the patient's body weight. More specifically, the range is from about 6.0 to about 36.0 mg/kg/day.

Examples of compounds useful in the present invention are lovastatin and simvastatin as well as their homologues. Also included are compounds classified as HMG Co-A inhibitors, as well as their homologues or analogues. Generally, these HMG Co-A inhibitors are known to lower serum cholesterol in humans. However, the present invention is not so limited. That is, an inhibitor of HMG Co-A or one of its homologues may work in the method of the present invention without necessarily lowering serum cholesterol. The invention focuses not on the compound's ability to lower cholesterol, but rather on the compound's ability to treat selected cancers, such as adenocarcinomas of the prostate, stomach, lung, breast and colon and certain sarcomas such as Ewing's sarcoma.

Also provided by the invention is a method of reducing PSA levels in a patient having prostatic adenocarcinoma comprising administration of an effective amount of a compound which is an inhibitor of HMG Co-A or a homologue or analogue of such an inhibitor. The invention also includes a method of reducing PSA in conjunction with another treatment modality. Additionally described is an appropriate unit dose ranging from about 100mg to about 2000mg.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph of concentration-dependence of lovastatin-induced growth arrest in human prostate cancer cell lines.

FIG. 2 is a graph of concentration-dependence of lovastatin-induced growth arrest in six defined human solid tumors in cell lines.

FIG. 3 is a graph of concentration-dependence of lovastatin-induced loss of clonogenicity in a human prostate carcinoma cell line.

FIG. 4 is a graph of concentration-dependent growth arrest following treatment of two human prostate carcinoma cell lines with simvastatin.

FIG. 5 is a graph of effect of lovastatin on plasma PSA level in a patient treated at 2mg/kg/day for 7 days.

FIG. 6 is a graph of effect of lovastatin on plasma PSA level in a patient treated for 2 cycles at 2mg/kg/day/7 days.

#### DESCRIPTION OF THE PREFERRED EMBODIMENT

Lovastatin induces cell death of certain susceptible human tumor types *in vitro* in a dose achievable *in vivo*. Clinical data presented here demonstrate anti-cancer activity of short course, high dose lovastatin as measured by decline in the level of the tumor marker PSA in patients with prostate cancer.

Data collected thus far indicate that patients with prostate cancer, both hormone-refractory and hormone-sensitive, and patients with gastric cancer are good candidates for the cytotoxic activity of lovastatin and related compounds. In addition, certain patients with breast cancer, Ewing's sarcoma, and other selected tumors respond to the anti-cancer activity of this class of drugs. *In vitro* testing is currently underway to facilitate selection of patients.

Lovastatin rapidly acts on the human prostatic carcinoma cell lines, PC-3, PC-3-M, DU-145 and LNCaP, and the LD 50s were all below 10  $\mu\text{g/ml}$  for exposures of 4 days. In the case of PC-3-M, there was complete loss of clonogenicity after exposure to 4  $\mu\text{g/ml}$  for 4 days. The term "clonogenicity", or immortality, refers to the ability of an isolated cell to produce progeny *in vitro*. Thus, in the case

of human prostate cancer, rapid tumor cell kill may be seen at blood levels which animal models and studies in human cancer patients suggest are tolerable in humans.

#### Dose and Schedule

5           In mammalian cells, lovastatin acts to arrest growth, not to kill cells, at drug levels as high as 100 times that currently used in patients. In the present invention, the currently approved hypercholesterolemic drug lovastatin is self-administered orally four times a day for seven days every  
10 28 days. Initial doses start at about 2 to 4 mg/kg/day. The clinical indication, dosage and schedule differ from the current use of this drug and other drugs in this class.

          The conventional clinical dosage for hypercholesterolemia ranges from 20-80 mg per day. With  
15 conventional management, lovastatin dose is not modified according to body weight or surface area. However, to use the present invention, the dose is adjusted based on body size, and 2mg/kg/day (0.5 mg/kg QID, where "QID" means "four times a day") is a preferred starting dose. Alternatively, other  
20 schedules, such as TID (three times a day) or BID (twice a day) could be employed.

          In the original clinical development of this drug, there were no phase 1 studies to determine dose-limiting toxicity in patients. With the doses in current clinical use,  
25 toxicities with potentially serious outcome are ordinarily limited to rhabdomyolysis and liver injury. The frequency of each of these toxicities is less than 1.5% at the currently recommended doses. In vitro studies have shown inhibition of lymphocyte proliferation at drug levels targeted by the phase  
30 1 study described below.

          To practice the invention, oral administration is preferred. An effective quantity of HMG Co-A inhibitor or related compound is employed in treatment. The dosage of the specific compound for treatment depends on many factors that  
35 are well known to those skilled in the art. They include for example, the route of administration and the potency of the particular compound. A preferred dosage for humans of about 70 kgs is from about 35 mg to about 910 mg in a single dose



taken four times a day. Generally the dose is from about 2 to about 52 mg per kg per day.

A preferred dosing schedule is an oral dose usually four times a day for a limited period, typically about 7 days. The schedule is preferably repeated at a suitable interval, usually at about 28-days with the first day of the first cycle counted as day one.

#### Recognized Toxicities of Lovastatin and Their Management

##### 1. Hepatic toxicity

Oral administration ensures high hepatic drug levels. In addition, the liver is a major site of lovastatin activation from the lactone to the more active acid form. Most of the drug is cleared by hepatic metabolism and biliary secretion. Also, the liver is the major site of cholesterol synthesis and thus the site at which lovastatin accomplishes most of its effect upon circulating cholesterol levels. Lovastatin can cause hepatocellular injury, but this is usually very limited in severity.

At the dose range given for hyperlipidemia (maximum of 80 mg/day), approximately 1.5% of patients will experience a three-fold rise in hepatic transaminase levels. In all cases, hepatic transaminase levels returned to normal within several weeks of discontinuation of lovastatin therapy.

##### 2. Rhabdomyolysis

Muscle pain associated with elevated creatine phosphokinase (CPK) levels have been reported. At a dose of 80 mg/Day, about 1.5% of patients will experience CPK elevations of  $\geq 1,000$  U/L (5 times normal). Clinically evident myopathy associated with prolonged elevation of CPK and muscle discomfort has been seen in less than 0.1% of cases.

##### 3. Lens Opacities

The development of lens opacities during the course of lovastatin therapy have been reported. However, these changes also occur spontaneously in this age group and at present blinded, randomized trials do not support an increased risk in patients on recommended doses of lovastatin.

Nevertheless, this side effect may emerge as significant with dose escalation.

#### 4. Idiosyncratic reactions

5 Lovastatin has been on the market for several years  
and more than one million patients have been treated with it.  
During that time, a number of reactions have been reported in  
one or a few patients that were not seen in preclinical  
testing or in the extensive clinical trials that preceded  
marketing approval. These have been so uncommon that the  
10 relationship of these reactions to lovastatin is at present  
unclear.

However, as the dose is escalated in practicing this  
invention, one or more of these rare events may occur with  
greater consistency. They include: alopecia, depression,  
15 bleeding, skin rash, anaphylaxis, arthralgia, Lupus-like  
syndrome, angioedema, urticaria, hemolytic anemia, leucopenia,  
and thrombocytopenia.

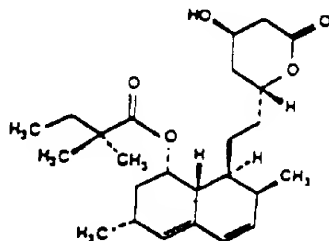
#### 5. Preclinical toxicities not noted in patients at conventional doses

20 In rabbits, but not mouse, rat, dog or monkey, lovastatin  
causes renal failure at peak blood levels of 8-10  $\mu\text{g/ml}$ . In  
rabbits, but not mouse, dog or monkey, lovastatin causes  
gallbladder necrosis. In dogs, but not mouse, rat, rabbit or  
monkey, lovastatin can cause testicular atrophy. In rat and  
25 mouse, lovastatin causes lesions in the nonglandular stomach  
which is a non-acid producing portion of an animal's stomach,  
presumably used to store food. Since humans do not have an  
equivalent of the nonglandular stomach, the relevance of this  
observation is not known.

#### 30 Therapeutic Administration

Lovastatin is approved for marketing in the U.S. and  
is currently one of the top ten drugs prescribed in the  
clinical setting. It is available as both 20 and 40 mg  
tablets for oral administration. As excipients, each tablet  
35 contains cellulose, lactose, magnesium stearate and starch.  
The 20 mg tablets contain FD & C blue dye number 2. The 40 mg  
tablet is green and contains both FD&C blue dye number 2 and  
yellow dye number 10. Tablets should be stored between 2 and

30 ° C, protected from light, and kept in a well-closed container. Simvastatin, recently been approved in the United States to treat elevated cholesterol, is represented by formula II



Compositions of the present invention are presented for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, eye drops, oral solutions or suspensions and water-in-oil emulsions containing suitable quantities or formulations of HMG Co-A inhibitors.

For oral administration, either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, HMG Co-A inhibitors are mixed into formulations with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methylcellulose, and functionally similar materials as pharmaceutical diluents or carriers.

Capsules are prepared by mixing the inhibitor or related compound with an inert pharmaceutical diluent and filling the mixture into hard gelatin capsule of appropriate size. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the inhibitor or related compound with an acceptable vegetable oil, light liquid petrolatum or other inert oil.

Fluid unit dosage forms for oral administration such as syrups, elixirs and suspensions can be prepared. The water-soluble forms can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydroalcoholic (ethanol) vehicle with suitable sweeteners

such as sugar and saccharin, together with an aromatic flavoring agent. Suspensions can be prepared with an aqueous vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

5           The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired pharmaceutical effect in association with the required  
10       pharmaceutical diluent, carrier or vehicle. Some examples of suitable unit dosage forms are tablets, capsules, pills, powder packets, wafers, granules, teaspoonfuls, tablespoonfuls, droppersful, ampoules, and vials.

          The following examples are illustrative, and not  
15       limitations of the invention. Those skilled in the art will promptly recognize appropriate variations from the procedures as to dosing, scheduling, indications and toxicity.

Examples

EXAMPLE 1

20           Cell lines of human prostate cancer cells were cultivated using methods well known to those of ordinary skill in the art. Varying doses of lovastatin from 0.001 to 100 micromoles per liter ( $\mu$ M) were administered to four such cell lines and compared against control cell lines. Of the  
25       experimental cell lines, three were hormone-independent (PC-3, PC-3-M, and DU 145) and one was hormone-sensitive (LNCaP). All four prostate cancer cell lines responded to lovastatin at doses from 1 to 100  $\mu$ M compared to controls. The response of the treated cancer cells did not correlate with hormone  
30       sensitivity of the cancer cells. See Fig. 1.

EXAMPLE 2

          Various human cell lines were cultivated using techniques well known to those of ordinary skill in the art. These cell lines were derived from cells of prostate carcinoma  
35       (PC-3/PC-3-M/DU 145), stomach cancer (AZ 521), pulmonary adenocarcinoma (A 549) and colon carcinoma (SW 620-AD). Concentrations of lovastatin varying from 0.01 to 100  $\mu$ M were applied to each of the six cell lines and the response was

compared to the controls as a percentage of growth. See Fig. 2. The data show good response to lovastatin dosages of 1 to 100  $\mu$ M. Thus, various adenocarcinomas are sensitive to lovastatin treatment.

5

## EXAMPLE 3

To demonstrate loss of clonogenicity in a cancer cell line, a human prostate carcinoma cell line (PC-3-M) was treated with doses of lovastatin varying from 0.5 to 100  $\mu$ M and compared against controls as a percentage of growth. The data indicate some loss of clonogenicity when the lovastatin dose was from 0.1 to 1  $\mu$ M and an extreme loss of clonogenicity at 10  $\mu$ M with absence of clonogenicity at dosages of 40 to 100  $\mu$ M. The exposure of the cell lines to lovastatin occurred over a four day period.

15

## EXAMPLE 4

Two human prostate carcinoma cell lines, PC-3 and DU 145, were treated with simvastatin, a lovastatin analogue which is also a product of Merck & Co. The concentration of simvastatin varied from 0.5 to 100  $\mu$ M. The growth of the cancer cell lines was compared to control cell lines as a percentage. The data indicate that at concentrations of 1 to 100  $\mu$ M of simvastatin, the cancer cell growth diminished substantially with both cell lines showing essentially zero growth after treatment with 100  $\mu$ M of simvastatin. See Fig. 4.

25

## EXAMPLE 5

In a clinical trial, a patient having prostatic adenocarcinoma was treated with 2mg/kg/day of lovastatin administered orally daily for 7 days. The patient's plasma PSA levels were determined. Pretreatment PSAs show an exponential increase. At the time of drug administration, the patient's blood level of PSA was approximately 700 nanograms per milliliter (ng/ml). After 7 days of treatment, the PSA had diminished to 600 ng/ml where it remained when tested on day 17 after treatment. See Fig. 5. A heavy bar shows the time interval of drug administration.

35

## EXAMPLE 6

In a clinical trial, a patient having prostatic adenocarcinoma was treated for two cycles at 2mg/kg/day for 7 days with the second cycle occurring 28 days later. The patient's plasma PSA levels were determined. The pretreatment PSA levels show an exponential increase from approximately 120 pretreatment until the treatment day. On the first day of treatment, the patient's PSA level was approximately 100 ng/ml. After the first cycle or 7 days of treatment, the patient's PSA level diminished to about 55 to 60 ng/ml. See Fig. 6.

## EXAMPLE 7

A Phase 1 Clinical Trial of short course, high dose lovastatin in the treatment of patients with cancer for whom there are no other therapeutic options of proven effectiveness is in progress.

The starting dose is 2mg/kg/day (0.5 mg/kg QID). The dose is escalated to 25.8 mg/kg/day. Each escalation is fixed at 2 mg/kg/day until a dose of 3 mg/kg QID is reached, after which the dose increases by 20% increments.

Dose escalation is monitored primarily with a series of pharmacodynamic parameters as well as toxicity signs and symptoms. Because this is a phase 1 trial, it is open to patients with any malignancy.

The lovastatin is administered QID for seven consecutive days. During the first week of the first cycle, patients are carefully monitored as outpatients. Therapy is repeated after a three week (21 day rest). Such 28 day cycles may be repeated until tumor progression has been documented or CTEP grade III or greater toxicity prevents further treatment. CTEP stands for Cancer Therapy Evaluation Program which those in the art recognize as a program under the National Cancer Institute that controls clinical trials.

A minimum of three patients are treated at each dose level and followed for one month before moving to the next dose level. Doses are based upon actual body weight.

	Dose per Kg/QID (Total Dose per Day)	% increase in dose
	Level 1 0.5 mg/Kg QID (2.0 mg/Kg/Day)	-
	Level 2 1.0 mg/Kg QID (4.0 mg/Kg/Day)	100
	Level 3 1.5 mg/Kg QID (6.0 mg/Kg/Day)	50
5	Level 4 2.0 mg/Kg QID (8.0 mg/Kg/Day)	33
	Level 5 2.5 mg/Kg QID (10.0 mg/Kg/Day)	25
	Level 6 3.0 mg/Kg QID (12.0 mg/Kg/Day)	20
	Level 7 3.6 mg/Kg QID (14.4 mg/Kg/Day)	20
	Level 8 4.3 mg/Kg QID (17.2 mg/Kg/Day)	20
10	Level 9 5.15 mg/Kg QID (20.6 mg/Kg/Day)	20
	Level 10 6.2 mg/Kg QID (24.8 mg/Kg/Day)	20
	Level 11 14.9 mg/Kg QID (29.8 mg/Kg/Day)	20
	Level 12 8.95 mg/Kg QID (35.8 mg/Kg/Day)	20
	Level 13 10.75 mg/Kg QID (43.0 mg/Kg/Day)	20
15	Level 14 12.9 mg/Kg QID (51.8 mg/Kg/Day)	20

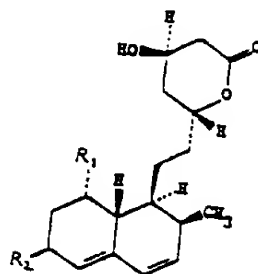
Because lovastatin is available in 20 and 40 mg tablets, the dose is rounded off to the nearest multiple of 20 mg. If, at any dose level, one patient develops CTEP grade III toxicity, then additional patients are entered at that dose level until at least 6 patients have been treated. If grade III or higher toxicity develops in 3 of the 6 patients entered at any given dose level, then no further dose escalation is to be made and the next lower lovastatin dose will be considered to be a maximally tolerated dose, and an additional three patients entered at this dose to confirm that it is safe. If a patient experiences a grade III toxicity but is responding to therapy, he may be retreated at the next lower dose level. A maximum of 60 patients are placed on this trial.

CTEP common toxicity criteria do not exist for rhabdomyolysis. Thus, it is necessary to set separate criteria for this toxicity. For this purpose, an elevation of CPK to 10 times normal or muscle pain sufficient to make daily activities difficult are regarded as equivalent to a CTEP grade III toxicity.

As the dose levels escalate, patients who entered at lower dose levels may have their dose increased on their next cycle. The maximal dose allowed will be one dose level lower than the current dose level being investigated. Although a QID schedule is preferred, other schedules, such as TID or BID could be used.

WHAT IS CLAIMED IS:

1. A method for treating an adenocarcinoma or a sarcoma in a mammal comprising administration of an effective amount of a compound of the formula I



- wherein R<sub>1</sub> is selected from a group consisting of a hydrogen atom, a hydroxy group, a 2-methylbutyryloxy group (-OCOCH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>) and a 2,2-dimethylbutyryloxy group (-OCOC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and R<sub>2</sub> is selected from a group consisting of a hydrogen atom and a methyl group.
2. The method of claim 1 wherein the compound is chosen from the group comprising lovastatin and simvastatin.
3. The method of claim 1 wherein the neoplasm is an adenocarcinoma.
4. The method of claim 3 wherein the adenocarcinoma is a member of the group consisting of adenocarcinoma of a prostate, stomach, lung, breast and colon.
5. The method of claim 3 wherein the adenocarcinoma is of a prostate gland.
6. The method of claim 1 wherein the neoplasm is an Ewing's sarcoma.
7. The method of claim 1 wherein the administration is oral.

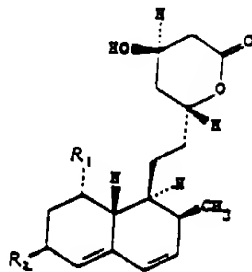


8. The method of claim 1 wherein the effective amount is from about 2.0 to about 52.0 mg/kg/day.

9. The method of claim 8 wherein the effective amount is about 6.0 to 36.0 mg/kg/day.

10. A method of diminishing an elevated prostate specific antigen level in a human comprising administration of an effective amount of lovastatin.

11. A method of reducing a prostate specific antigen level in a patient having prostatic adenocarcinoma comprising co-administration of an effective amount of a compound of formula I



wherein  $R_1$  is selected from a group consisting of a hydrogen atom, a hydroxy group, a 2-methylbutyryloxy group ( $-\text{OCOCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ ) and a 2,2-dimethylbutyryloxy group ( $-\text{OCOC}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$ ) and  $R_2$  is selected from a group consisting of a hydrogen atom and a methyl group, and

wherein said administration is in conjunction with another treatment modality.

12. The method of claim 11 wherein the inhibitor is selected from a group comprising lovastatin and simvastatin.

13. The method of claim 11 further comprising detecting a level of prostate specific antigen of the patient.

14. The method of claim 13 wherein the detected prostate specific antigen level is from the patient's blood.

15. The method of claim 11 wherein the other treatment modality includes a dose of a chemotherapeutic agent.
- 5 16. The method of claim 15 wherein the dose of the chemotherapeutic agent is correlated with a level of prostate specific antigen of the patient.
- 10 17. The method of claim 11 wherein the administration is oral.
18. The method of claim 11 wherein the effective amount is from about 2.0 to about 52.0 mg/kg/day.
- 15 19. The method of claim 18 wherein the effective amount is about 6.0 to 36 mg/kg/day.
20. A pharmaceutical composition in unit dose form comprising:  
one or more pharmaceutically acceptable excipients; and  
20 an amount of a compound of formula 1 effective to treat cancer in a mammal to whom one or more unit doses of said composition are administered.
- 25 21. The composition of claim 20 wherein the composition is adapted for oral administration.
22. The composition of claim 20 wherein the amount of the compound is from about 40 mg to about 2000 mg.

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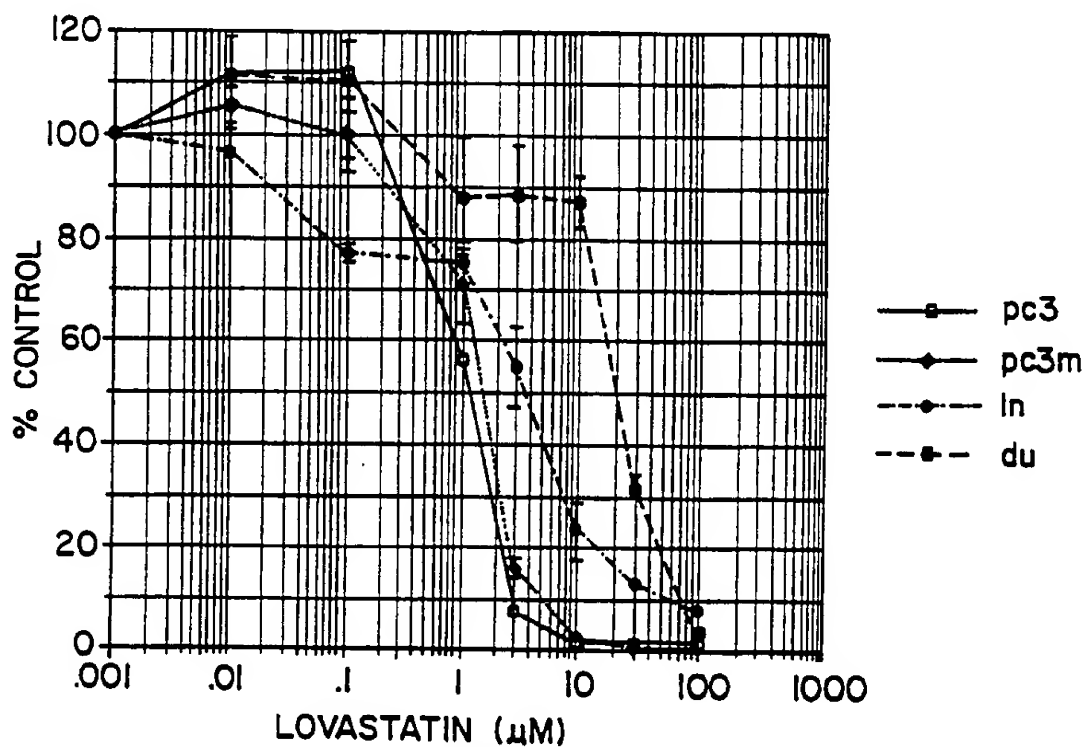


FIG. 1.

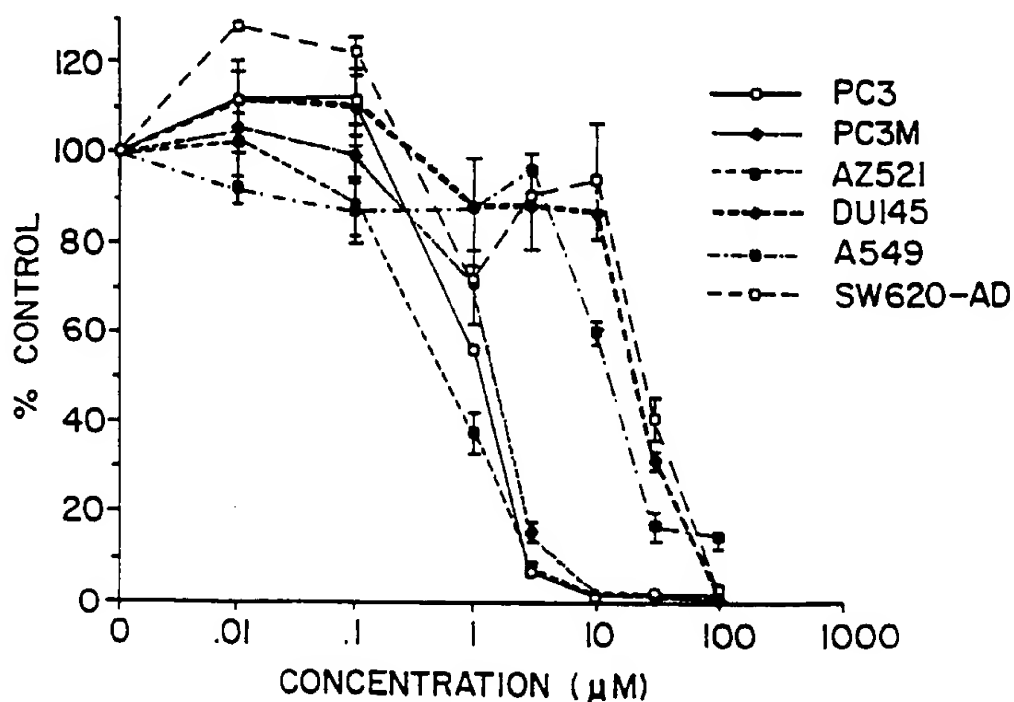


FIG. 2.

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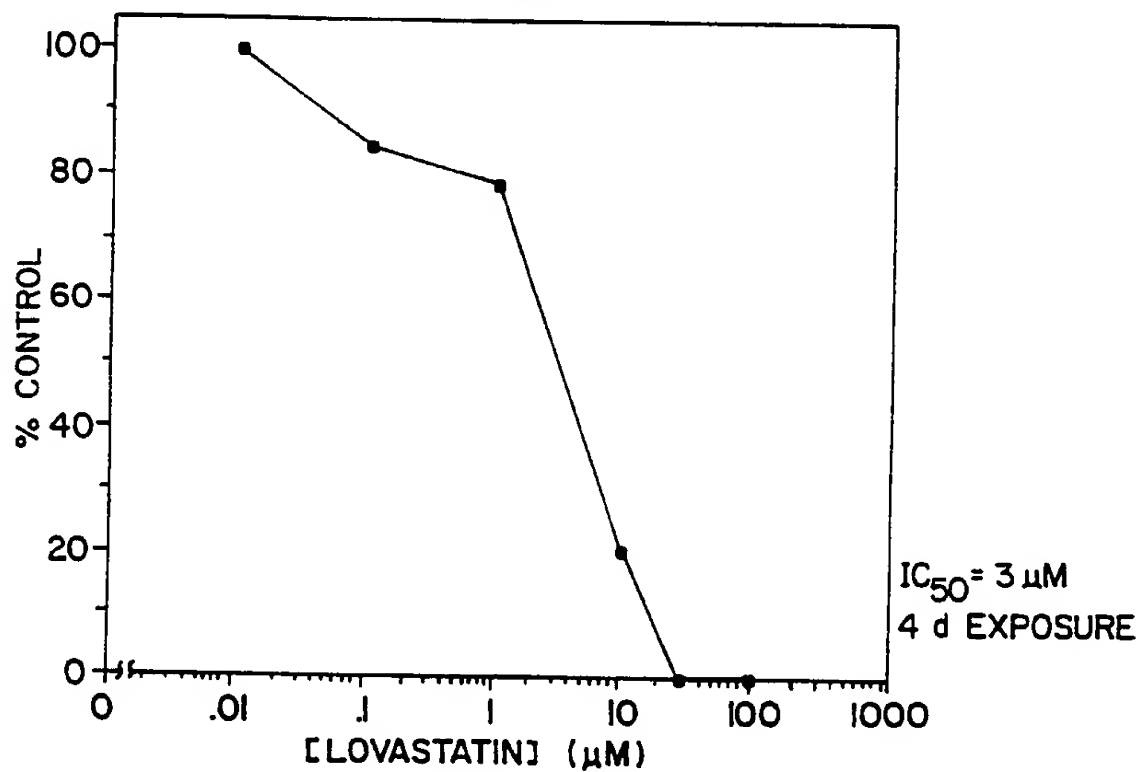


FIG. 3.

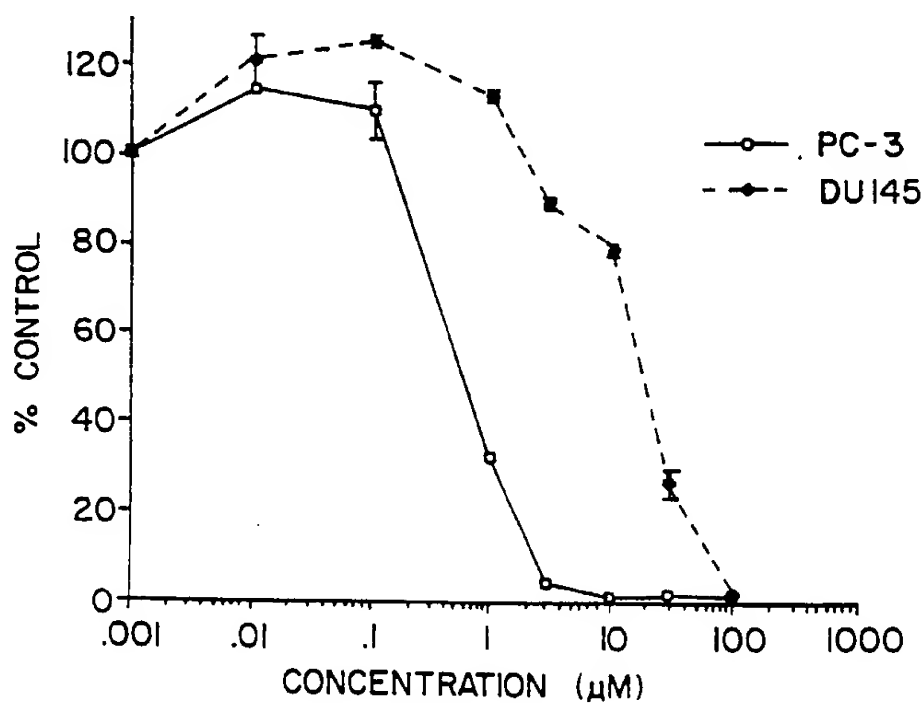
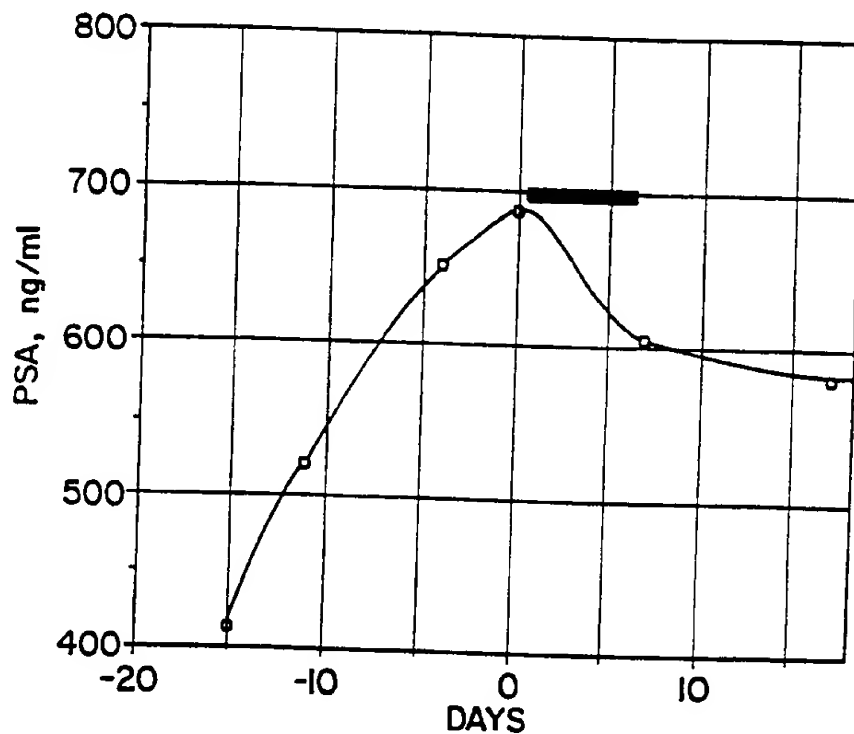
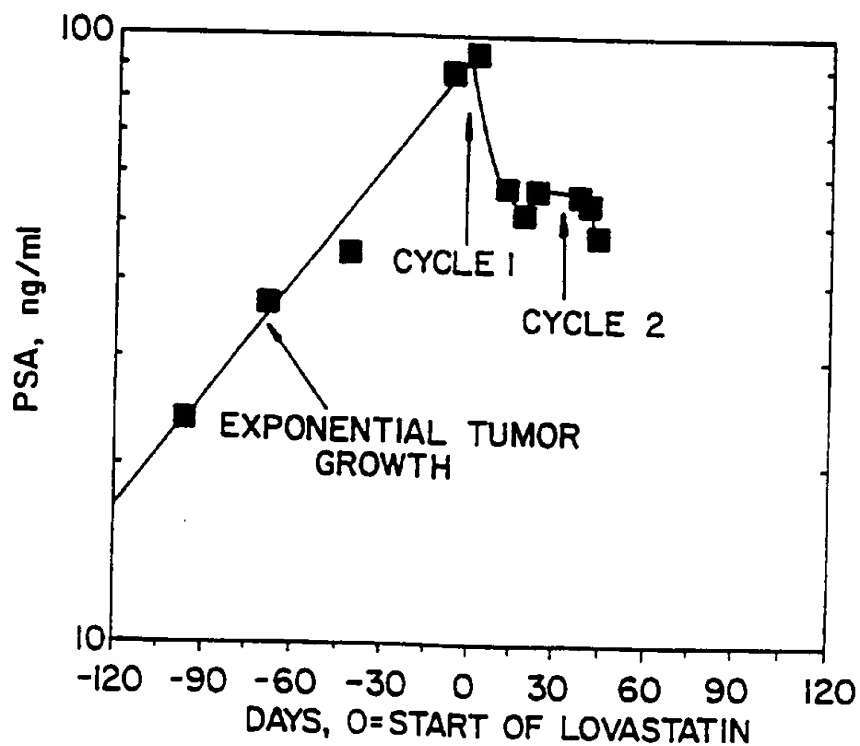


FIG. 4.

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**FIG. 5.****FIG. 6.**  
**SUBSTITUTE SHEET**

**I. CLASSIFICATION OF SUBJECT MATTER** (If several classification symbols apply, indicate all)\*

According to International Patent Classification (IPC) or to both National Classification and (IPC)

Int.Cl. 5 A61K31/35

**II. FIELDS SEARCHED**Minimum Documentation Searched<sup>1</sup>

Classification System

Classification Symbols

Int.Cl. 5

A61K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>1</sup>**III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>2</sup>**

Category <sup>3</sup>	Citation of Document, <sup>4</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	THE JOURNAL OF CLINICAL INVESTIGATION vol. 76, no. 5, November 1985, pages 1748 - 1754 MALTESE, W.A. ET AL 'SUPPRESSION OF MURINE NEUROBLASTOMA GROWTH IN VIVO BY MEVINOLIN, A COMPETITIVE INHIBITOR OF 3-HYDROXY-3-METHYLGUTARYL-COENZYME A REDUCTASE' see the whole document ---	1,2, 20-22
X	CANCER COMMUNICATIONS vol. 3, no. 5, May 1991, pages 141 - 147 SEBTI, S.M. ET AL 'LOVASTATIN, A CHOLESTEROL BIOSYNTHESIS INHIBITOR, INHIBITS THE GROWTH OF HUMAN H-ras ONCOGENE TRANSFORMED CELLS IN NUDE MICE' see the whole document ---	1-3,8, 20-22

-/-

<sup>10</sup> Special categories of cited documents:

- "A" documents defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" documents which may throw doubts on priority claim(s) or which is cited to establish the publication date of another claim or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

**IV. CERTIFICATION**

Date of the Actual Completion of the International Search

01 SEPTEMBER 1993

Date of Mailing of this International Search Report

16.03.93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

MAIR J.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CLINICAL AND EXPERIMENTAL METASTASIS vol. 7, no. 5, 1989, pages 517 - 523 KORT, M.J. ET AL 'MODULATION OF METASTATIC ABILITY BY INHIBITION OF CHOLESTEROL SYNTHESIS' see the whole document	1-4, 8, 9, 20-22
P, X	--- GASTROENTEROLOGY vol. 103, no. 3, September 1992, pages 982 - 989 SUMI, S. ET AL 'INHIBITION OF PANCREATIC ADENOCARCINOMA CELL GROWTH BY LOVASTATIN' see the whole document	1-3, 8, 9
P, X	--- BRITISH JOURNAL OF CANCER vol. 66, no. 2, August 1992, pages 304 - 310 MIKULSKI, S.M. ET AL 'SYNERGISM BETWEEN A NOVEL AMPHIBIAN OOCYTE RIBONUCLEASE AND LOVASTATIN IN INDUCING CYTOSTATIC AND CYTOTOXIC EFFECTS IN HUMAN LUNG AND PANCREATIC CARCINOMA CELL LINES'	1-4
P, A	see the whole document	11, 15
X	Week 8143, Darwent Publications Ltd., London, GB; AN 81-78653D & JP, A, 56 115 717 (ENDO, AKIRA) 11 September 1981 see abstract	20-22
A	---	4, 5, 10-14, 17-19
P, X	CANCER RESEARCH vol. 52, no. 16, 15 August 1992, pages 4348 - 4355 SOMA, M.R. ET AL 'SIMVASTATIN, AN INHIBITOR OF CHOLESTEROL BIOSYNTHESIS, SHOWS A SYNERGISTIC EFFECT WITH N,N'-BIS(2-CHLOROETHYL)-N-NITROSOUREA AND BETA-INTERFERON ON HUMAN GLIOMA CELLS'	1, 2, 8, 9
P, A	see the whole document	11, 15
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RE DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claims No.
X	JOURNAL OF CELLULAR BIOCHEMISTRY vol. 50, no. 16H, 1992, pages 1 - 8 KELLOFF, G.J. ET AL 'INTRODUCTORY REMARKS: DEVELOPMENT OF CHEMOPREVENTIVE AGENTS FOR PROSTATE CANCER'	1-5, 10
A	see the whole document especially table I, page 5 and page 7, column 1, lines 14-27 -----	11-19



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/04454

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 1-19 are directed towards a method of treatment of the human or animal body, the search has been carried out and based upon the alleged effects of the compounds.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6A(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.